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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/918,407	08/26/97	ROTH J	INGN:050/HYL

HM22/0315

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EXAMINER	
SANDALS,W	
ART UNIT	**PAPER NUMBER**
1636	9

DATE MAILED: 03/15/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/918,407	Applicant(s) Roth et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Aug 26, 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-135* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-135* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7*

☒ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Rite Eg

Interview Summary

Application No.	Applicant(s)
08/918,407	Roth et al.
Examiner	**Group Art Unit**
WILLIAM SANDALS	1636

All participants (applicant, applicant's representative, PTO personnel):

(1) *WILLIAM SANDALS* (3) _____

(2) *Steve Highlander, Esq.* (4) _____

Date of Interview *Mar 9, 1999*

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☒ was reached. ☐ was not reached.

Claim(s) discussed: *1 and 2*

Identification of prior art discussed:
None

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
We discussed the restriction requirement. An election of species was made to the p53 gene. We discussed the preliminary amendment in Paper number 4, filed on March 9, 1998 which contained improper amendments to claims 1 and 2. It was agreed that the improper amendments of claims 1 and 2 would be designated as "not entered".

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. ☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

DETAILED ACTION

Election/Restriction

1. This application contains claims directed to the following patentably distinct species of the claimed invention: Claims 1-3 are drawn to a method of killing a cell comprising contacting a cell with a p53 protein or gene and a DNA damaging agent. The species are the p53 protein and the p53 gene.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 4-135 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to

be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

2. During a telephone conversation with Steven Highlander, Esq. on March 9, 1999, a provisional election was made with traverse to prosecute the invention of the method of killing a cell, comprising contacting a cell with a p53 gene and a DNA damaging agent, claims 1-3. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-3 as they pertain to the method of killing a cell, comprising contacting a cell with a p53 protein and a DNA damaging agent are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

4. Applicant's claim for domestic priority under 35 U.S.C. 120 is acknowledged. However, the non-provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-135 of this application. No disclosure of a combination of p53

gene and a DNA damaging agent in a method of killing cells, nor of a non-viral vector is found in the priority document US Application number 08/145,826, filed October 29, 1993. Disclosure is found which describes a combination of p53 gene and a DNA damaging agent in a method of killing cells, and a non-viral vector in priority document US Application 08/233,002, filed April 25, 1994. Therefore, priority for the instant claimed invention is established as found in the priority document US Application 08/233,002, filed April 25, 1994.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

6. Two citations in the PTO form 1449 submitted on March 9, 1999, listed as "reference designation" numbers C161 and C162 have not been considered since they are US Application numbers, and as such are non-published, and are not proper entries in PTO-1449. These references are priority documents of the instant application, and have properly been used to claim priority in the first paragraph of the instant specification.

Drawings

7. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

8. The use of the trademarks Triton X-100, Vectastain Elite, and Cytoseal have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-25, 46-61, 67-82, 86, 115-124 and 127-130 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cells in culture, does not reasonably provide enablement for cells *in vivo*. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method of killing a cell comprising contacting a cell with a p53 protein or gene and a DNA damaging agent. While applicants have shown an *in vitro* method of killing a cell comprising contacting a cell with a p53 gene and a DNA damaging agent, they have not demonstrated any *in vivo* method of killing a cell comprising contacting a cell with a p53 gene and a DNA damaging agent. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve the practice of gene therapy, the *in vivo* administration of a gene for treatment.

b- Guidance and examples are provided for *in vitro* practice only of the claimed invention.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

11. Claims 26-31, 41-45, 62-66, 83-85, 92-114, 125-126 and 131-135 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of killing a cell comprising contacting a cell with a p53 protein or gene and a DNA damaging agent in a cell within an animal. While applicants have shown an *in vitro* method of killing a cell comprising contacting a cell with a p53 gene and a DNA damaging agent, they have not demonstrated any *in vivo* method of killing a cell comprising contacting a cell with a p53 gene and a DNA damaging agent. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve the practice of gene therapy, the *in vivo* administration of a gene for treatment.

b- Guidance and examples are provided for *in vitro* practice only of the claimed invention.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

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e- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 6, 9-11 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claim 6 (and dependent claims 9-11) recites the limitation "recombinant adenoviral vector" in line 2. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 66 recites the limitation "to the animal" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Double Patenting

16. Claims 1-135 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-105 of U.S. Patent No. 5,747,469. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed method of killing a cell, comprising contacting a cell with a p53 gene and a DNA damaging agent contains the same elements as the patented method of US Patent No. 5,747,469. Other common elements of the instant claimed invention and in US Patent No. 5,747,469 are that the p53 gene may be in a viral vector, the p53 gene may be linked to a promoter, and the cells may be various tumor cells. Commonly claimed is a method of killing a tumor cell in a patient in need thereof, comprising administering to said tumor cell a therapeutically effective amount of a viral vector comprising a p53 gene operatively linked to a promoter, and numerous well known DNA damaging agents.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

18. Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Lowe et al.

The claim is drawn to a method of killing a cell comprising contacting a cell with a p53 gene and a DNA damaging agent.

Lowe et al. taught a method of killing a cell comprising contacting a cell with a p53 protein or gene and a DNA damaging agent. Lowe et al. taught each and every aspect of the instant invention, thereby anticipating Applicant's invention.

19. Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Clarke et al.

The claim is drawn to a method of killing a cell comprising contacting a cell with a p53 gene and a DNA damaging agent.

Clarke et al. taught a method of killing a cell comprising contacting a cell with a p53 protein or gene and a DNA damaging agent. Clarke et al. taught each and every aspect of the instant invention, thereby anticipating Applicant's invention.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 2-25, 46-61, 67-82, 86, 115-124 and 127-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowe et al. or Clarke et al. in view of Tischler et al., Will et al. and Gregory et al.

The claims are drawn to a method of killing a cell comprising contacting a cell with a p53 gene and a DNA damaging agent, where the agent may be X-rays, UV irradiation, gamma irradiation, microwaves, adriamycin, 5-flourouracil, etoposide, campothecin, actinomycin-D, mitomycin C, or cisplatin. The p53 gene may be in a non-viral vector, which may be a naked DNA plasmid or a plasmid in a liposome or in a adenoviral vector. The adenoviral vector may be deleted for one essential gene, which may be the E1A and E1B regions. The cell may be a human tumor cell. The plasmid may have a cytomegalovirus promoter and an SV40 polyadenylation signal.

Lowe et al. (see the entire article) and Clarke et al. (see the entire article) taught a method of killing a cell comprising contacting a cell with a p53 gene and a DNA damaging agent, where the agent may be X-rays, gamma irradiation, or etoposide. The p53 gene was in a non-viral vector, which may be a naked DNA plasmid. The cell may be a human tumor cell.

Lowe et al. and Clarke et al. did not teach that the DNA damaging agent may be UV irradiation, microwaves, adriamycin, 5-flourouracil, campothecin, actinomycin-D, mitomycin C, or cisplatin, nor that the vector may be an adenoviral vector which may be deleted for one essential gene, which may be the E1A and E1B regions, nor that the plasmid may have a cytomegalovirus promoter and an SV40 polyadenylation signal.

Tischler et al. taught that the DNA damaging agent was X-rays, UV irradiation, gamma irradiation, microwaves, adriamycin, 5-flourouracil, etoposide, campothecin, actinomycin-D, mitomycin C, or cisplatin.

Wills et al. (see the entire article) and Gregory et al. (see the entire article) taught that an adenoviral vector expressing the p53 gene may be deleted in E1A or E1B, which contained a CMV promoter.

The use of an SV40 polyadenylation signal sequence and encapsulation of the vector in a liposome are arbitrary choices within the purview of an ordinary skilled artisan and, lacking unexpected results, are not deemed to make a patentable distinction to the instant claimed invention.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Lowe et al. or Clarke et al. with Tischler et al., Will et al. and Gregory et al. because they were all investigating the effects of p53 on cell death. The adenoviral vectors of Will et al. and Gregory et al. were equivalent to the plasmid vectors of

Lowe et al. or Clarke et al. or Tischler et al. for the purposes of introducing the p53 gene into cells to study cell death.

One of ordinary skill in the art would have been motivated at the time of the instant invention to combine the teachings of Lowe et al. or Clarke et al. with Tischler et al., Will et al. and Gregory et al. because they were all inserting p53 containing vectors into cells to investigate the effects of p53 gene on cell death. Lowe et al., Clarke et al. and Tischler et al. showed that the combination of DNA damaging agents with the p53 gene produced cell killing. Tischler et al. provided a larger assortment of obvious DNA damaging agents in combination with the p53 gene, and the adenoviral vectors of Will et al. and Gregory et al. were equivalent to the plasmid vectors of Lowe et al. or Clarke et al. or Tischler et al. for the purposes of introducing the p53 gene into cells to study cell death. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Lowe et al. or Clarke et al., Tischler et al., Will et al. and Gregory et al.

Conclusion

22. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
March 11, 1999

NANCY DEGEN
PRIMARY EXAMINER